REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Initially, the Applicant's representative wishes to express his appreciation to the Examiner for their discussion and review of proposed amended claims today. The foregoing amendments correspond to the amendments proposed and discussed with the Examiner.

Specifically, claims 1-17 and 19-24 are cancelled without prejudice.

Claim 18 has been amended along the lines suggested by the Examiner in the Official Action. Please see the last complete paragraph on page 3 of the Action.

In view of the foregoing, the rejection of claims 17-18 and 25-27 under 35 USC 112, first paragraph, is deemed to be overcome.

Claims 25-27 have been amended to specify the specific symptom and result of the performance of the method of claim 18.

These amendments are deemed to further limit claim 18 and are deemed to overcome the objection to claims 25-27 set forth on pages 2-3 of the Action.

Turning to the patentability grounds of rejection, claims 17-18 and 25-27 are rejected under 35 USC 102 as anticipated by Akimoto, Morishita or Nakamura for the reasons set forth on pages 9-11 of the Action. This ground of rejection is deemed to be overcome as applied to the amended claims.

Akimoto describes that HGF enhances learning and memory abilities of mice. In Akimoto, the learning and memory abilities of mice were studied by administering HGF to normal (non-diseased) mice.

On the other hand, the present invention relates to a method of treating cerebral embolism-induced cerebrovascular hyperpermeability. Akimoto neither discloses nor suggests that cerebral embolism-induced cerebrovascular hyperpermeability is suppressed by HGF.

The present application demonstrates that cerebral embolism-induced cerebrovascular hyperpermeability is suppressed *in vivo* by injecting HGF. That is, in the Experiments of the present application, HGF is injected to rats suffering from the symptom (diseased rats). Please see pages 16-25.

Therefore, the test of the present application is different in significance from that of Akimoto in which the effect of HGF to behavior of normal mice is studied.

Morishita (W097/07824, US 6,248,722) describes that coronary endothelial cells grow and the number of minute blood vessels increases by a HGF gene.

However, Morishita neither discloses nor suggests a method of treating cerebral embolism-induced cerebrovascular hyperpermeability by injecting HGF into the cerebral ventricles.

It has been known that a substance, e .g. VEGF, which increases blood endothelial cells, causes vascular hyperpermeability (c.f. Arch Dermatol., 2002; 138: 791-796 (Reference 1) enclosed).

Since Morishita describes that blood endothelial cells increase by HGF, the person skilled in the art will generally conceive that HGF will bring out vascular hyperpermeability.

However, although HGF was known to cause vascular hyperpermeability, HGF unexpectedly suppresses cerebral embolism-induced cerebrovascular hyperpermeability.

The function/effect of suppressing cerebral embolism-induced cerebrovascular hyperpermeability is unobvious over MORISHITA to the person skilled in the art.

Nakamura describes a method for treating of disorder in brain and nerve comprising administration of HGF.

However, Nakamura simply describes in the working Examples that HGF mRNA increases in brain after occurrence of cerebral ischemia and HGF acts *in vitro* as a survival factor of nerve cells. Namely, there is no experimental evidence in Nakamura what role is played by endogeneous or exogeneous HGF.

Further, Nakamura neither describes nor suggests the action of HGF to cerebral embolism-induced cerebrovascular hyperpermeability.

On the other hand, the subject matter of the present invention is directed to a method of treating a mammal suffering from cerebral embolism-induced cerebrovascular hyperpermeability by injecting HGF into the cerebral ventricle.

From the disclosure in Nakamura that HGF mRNA increases in brain after occurrence of cerebral ischemia, and that HGF acts as a survival factor of nerve cells, the person skilled in the art will be unable to conceive at all that cerebral embolism-induced cerebrovascular hyperpermeability can be suppressed by injecting HGF into the cerebral ventricles.

The symptom caused by cerebral embolism-induced cerebrovascular hyperpermeability is mainly cerebral edema. In cerebral edema, brain water unusually increases. That is, cerebral edema represents the state in which the blood-brain barrier (BBB) disrupts due to cerebral embolism, and as a result water and serum protein leak out from cerebral vessel to intercelluar space (i.e. cerebrovascular hyperpermeability) so that cerebral tissue becomes cerebral edema.

On the other hand, cerebral infarction represents the state in which necrosis is induced in cerebral tissue due to cerebral ischemia. Brain is a closed space, and cerebral infarction is caused because cerebral tissue is strongly pressed by cerebral edema for a long time. However, cerebral edema does not mean occurrence of cerebral infarction. To prove this, the Applicant submits herewith a Rule 1.132 Declaration executed by Dr. Satoshi Takeo.

A Rule 1.132 Declaration executed by Dr. Satoshi Takeo

Methods of experiment in the Rule 1.132 Declaration are the same as Experimental Example 1 on page 16, line 13 to page 19, line 28 in the present specification.

Fig. 1 of the Rule 1.132 Declaration shows a behavior disorder of animal suffering from cerebral embolism-induced cerebrovascular hyperpermeability (a behavior disorder caused by an invasive operation of cerebral embolism) observed for a certain period of time. It is apparent from Fig .1 that a behavior disorder is caused by cerebral embolism with microspheres. Since there is no difference of a behavior disorder between HGF- treated groups and HGF -untreated groups, it is apparent that the same degree of cerebral embolism is induced in all groups.

Since a behavior disorder disappears 12 days after inducing of cerebral embolism, it is apparent that irreversible necrosis (cerebral infarction) is not induced according to this test.

Fig. 2 of the Rule 1.132 Declaration shows the change over time of the leakage area of FITC-albumin in an animal suffering from cerebral embolism-induced cerebrovascular hyperpermeability.

It is apparent from Figs. 1 and 2 that the leakage amount of FITC-albumin does not correlate with a behavior disorder caused by an invasive operation of cerebral embolism.

Fig. 3 of the Rule 1.132 Declaration is identical with Fig.1 of the specification as originally filed.

Fig. 3 shows the effect of HGF treatment on the leakage area of FITC-albumin. It is apparent that HGF almost completely inhibits the leakage of FITC-albumin in the HGF-treated rats.

Fig .4 of the Rule 1.132 Declaration shows the brain water and cation contents in the rats on day 7 after the embolization. In the animals suffering from cerebral embolism-induced cerebrovascular hyperpermeability, the brain water, sodium ion and calcium ion remarkably increase.

These increases show that the symptom of cerebral edema is present. In the HGF- treated groups, increase of the brain water, sodium ion and calcium ion is significantly suppressed. These results demonstrate that, in the animals suffering from cerebral embolism-induced cerebrovascular hyperpermeability, cerebral edema is present, and HGF is effective for suppressing cerebral edema.

In the case where cerebral edema is treated as soon as possible, the induction of cerebral infarction will be able to be prevented.

Development of drugs to treat cerebral edema has been demanded. However, under the present conditions, for example, the intravenenous injection of glycerol or mannitol is conducted so that brain water is induced to a blood vessel by elevation of osmotic pressure of blood vessel.

Accordingly, the method of the present invention for treating the hyperpermeability is useful and is neither described nor suggested. The method of the present invention is quite different from that of treating cerebral infarction in Nakamura.

Fig. 5 of the Rule 1.132 Declaration shows the results of escape latency in the water maze test. The present results are identical with those shown in Tables 1-3 of the specification as originally filed. It is apparent that although spatial memory and learning function lowers by cerebral embolism-induced cerebrovascular hyperpermeability and cerebral edema, the lowering of spatial memory and learning function can be reduced by administering HGF.

In view of the foregoing, it is respectfully submitted that the amended claims are not anticipated under 35 USC 102 by any one of the cited references.

Lastly, claims 17-18 and 25-27 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 5, 7-8, 10 and 12-13 of USP 6,699,837. This ground of rejection is respectfully traversed as applied to the amended claims.

The present application relates to a method of treating cerebral embolism-induced cerebrovascular hyperpermeability.

As mentioned above, a method of treating cerebral embolism-induced cerebrovascular hyperpermeability is quite different from a method of promoting survival of neurons according

to the claims of USP 6,699,837. Moreover, it is noted that USP '837 only contains claims 1-3. Thus the rejection based upon claims 5, 7-8, 10 and 12-13 is not understood. A copy of claims 1-3 are enclosed as Reference 2.

Accordingly, it is respectfully submitted that the amended claims overcome the rejection on the ground of obviousness-type double patenting over USP 6,699,837.

Lastly, it is noted that the Examiner has not considered JP 2003-506368, i.e. Reference AF in the IDS dated April 13, 2006. An English language abstract of the reference was filed on the same date as reference AG, i.e. WO 01/09121. Consideration is respectfully solicited.

In view of the foregoing, it is believed that each ground of objection and rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Respectfully submitted,

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